Organic Chemistry Insights

ORIGINAL RESEARCH

Utility of 4,5-Diphenylimidazol-2-thione in Synthesis of Fused Heterocyclic Ring Systems with Biological Interest

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Abstract The reaction of 4,5-diphenylimidazol-2-thione **1** with chloroacetic acid in presence of acetic acid and sodium acetate afforded 5,6-diphenylimidazo [2,1-*b*]thiazole-3-one **3**. Compound **3**, when treated with acetic anhydride in presence of sodium acetate, dimethyl formamide dimethylacetal (DMFDMA), thiophene-2-carbaldehyde and 2-thenylidene activated nitriles gave 5,6-diphenylimidazo[2,1-*b*] thiazole derivatives **4, 6, 8** and 7,8-diphenyl imidazo[2,1-*b*] thiazolo [2,3-*b*] pyran derivatives $\mathbf{9}_{e,f}$, **10**. Claisen condensation of compound **4** with diethyl oxalate gives 7,8-diphenylimidazo [2,1-*b*] thiazolo [2,3-*b*]-4-pyron derivatives $\mathbf{5}_{a,b}$. While, 6,7-diphenylimidazo[2,1-*b*] thiazolo[2,3-*c*] oxazole or (N-phenylpyrazole) $\mathbf{7}_{c,d}$ were obtained directly upon reaction of 6 with hydroxylamine hydrochloride and phenyl hydrazine. Compound **1** reacted with α-chloroacetylacetone and α-chloroethylacetoacetate to give 2-acetyl or (2-ethoxycarbonyl) 3-methyl-5,6-diphenylimidazo[2,1-*b*] thiazole $\mathbf{12}_{h,i}$. Treatment of 12_h with thiophene-2-carbaldehyde led to the formation of 3-methyl-5, 6-diphenyl-2(2-thenylidene-2-propenoyl) imidazo[2,1-*b*]thiazole $\mathbf{13}_h$. Compound $\mathbf{13}_h$ react with each of 2-chlorophenyl hydrazine and benzamidine hydrochloride to give $\mathbf{14}_h$ and $\mathbf{15}_h$. Cyclocondensation of $\mathbf{12}_h$ with hydroxylamine hydrochloride and hydrazine hydrate gave $\mathbf{16}_j$ and $\mathbf{16}_k$. The newly synthesized compounds were tested for antibacterial and antifungal activity. Most of the tested compounds showed activity toward fungi while many of these did not have activity toward bacteria.

Keywords: 4,5-diphenylimidazol-2-thione, heterocyclic ring system, antibacterial, antifungal

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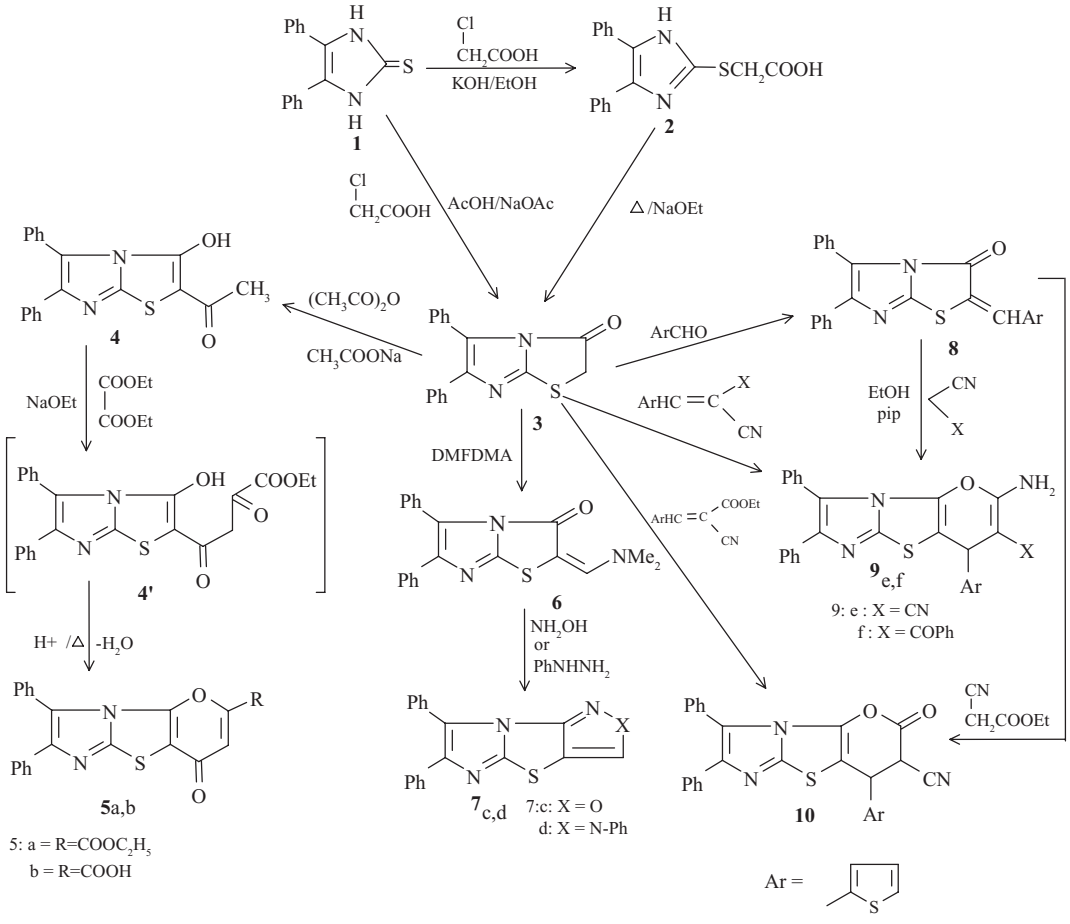
Introduction

Identification of novel compounds that effectively treat both infectious and inflammatory states, without adverse side effects remains a major challenge in biomedical research. The use of several drugs in combination is often problematic, in patients with impaired liver or kidney functions due to drug-drug interaction. In addition, from the pharmaco-economic cost-effectiveness stand point, and seeking better patient compliance, a dual anti-inflammatory-antimicrobial agent with minimum adverse effects and high safety margin is highly desirable. Compounds containing imidazo[2,1-*b*] thiazole functionality have been reported to exhibit anti-inflammatory, antimicrobial and cardiotonic selective agonist properties for the human orphan nuclear receptor CAR(constitutive androstane receptor) and diuretic agents.[1–4] This promted us to construct compounds containing both the imidazo[2,1-*b*] thiazoles and heterocyclic ring systems. We also prepared hybrid compounds between the pyrazollin or pyrimidine and the imidazo[2,1-*b*] thiazole nucleus in order to investigate the effect of such molecular variation on the antibacterial and antifungal activities.

Results and Discussion

4,5-Diphenylimidazol-2-thione **1** reacted with chloroacetic acid in ethanolic KOH[5] formed 2-s-methylcarboxylic acid **2**. Cyclization of **2** in ethanol in presence of sodium ethoxide gave 5,6-diphenylimidazo[2,1-*b*] thiazol-3-one **3** (Scheme 1). Compound **3** was also synthesized by cycloondensation of **1** with chloroacetic acid in the presence of acetic acid and sodium acetate[6] via an initial dehydrochlorination followed by loss of water. The proposed structure of **3** was proved both by elemental analysis and spectral data. Its IR and ^{1}H-NMR spectra showed the absorptions corresponding to



Scheme 1.

carbonyl group, methylene and aromatic protons. When heated **3** with acetic anhydride and sodium acetate[7] furnished the respective 2-acetyl-3-hydroxy-5,6-diphenylimidazo[2,1-*b*] thiazole **4**. Its IR spectrum displayed a strong hydrogen-bonded carbonyl absorption in the region 1630 cm^{-1} and a weak and broad hydroxyl absorption at 3200 cm^{-1}. In the ^{1}H-NMR spectrum one proton singlet in a low magnetic field δ 13.20 was observed for **4** which could be ascribed to the hydroxyl proton.

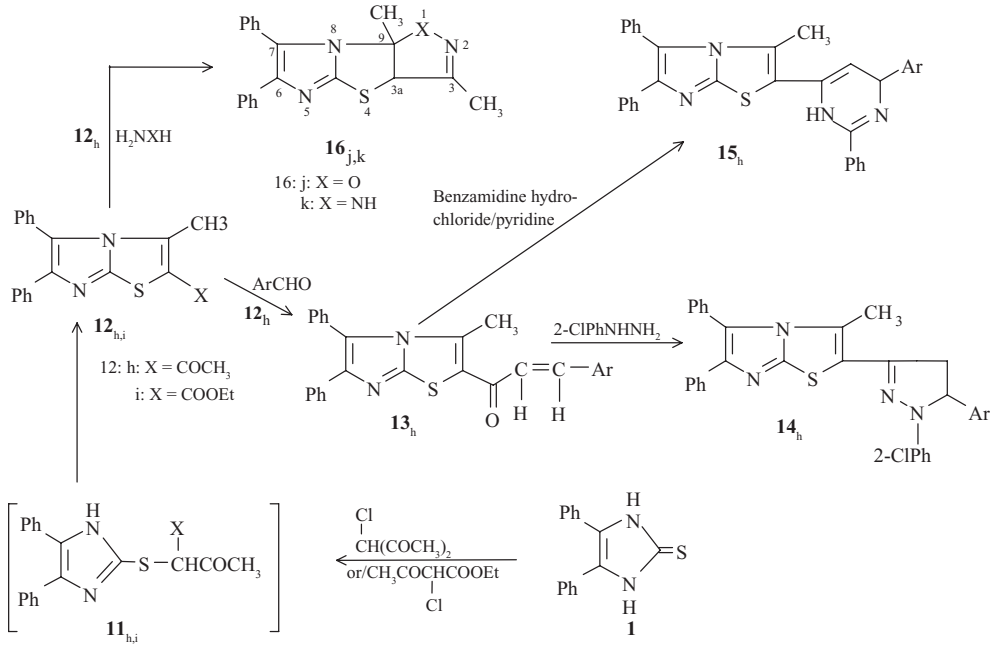
Claisen condensation of **4** with diethyl oxalate in the presence of sodium ethoxide[8] provided an intermediate "β-diketone" **4**' which was cyclized to give the mixture of an 7,8-diphenyl imidazo [2,1-*b*] thiazolo [2,3-*b*] pyran-2 ethoxycarbonyl-4-one $\mathbf{5}_a$ and 7,8-diphenyl imidazo [2,1-*b*] thiazolo [2,3-*b*] pyran-2-carboxylic acid-4-one $\mathbf{5}_b$. Compound **5**a on acid hydrolysis afforded the corresponding acid $\mathbf{5}_b$. The IR spectra of **5**a,b displayed characteristic absorption band for pyrone ring carbonyl in the region 1665 and 1660 cm^{-1}, the C—O—C stretching bond mode in the region 1135 and 1170 cm^{-1} and C—H the typical deformation in the 870 and 930 cm^{-1} region[9,10] observed for various derivatives of chromones. The ^{1}H-NMR spectra **5**a,b singlet for the proton pyrone ring at δ 6.98 and δ 6.00 were consistent with these structure.

The condensation of **3** with dimethyl formamide dimethylacetal (DMFDMA)[11] gave 2-dimethylaminomethylene-5,6-diphenylimidazo [2,1-*b*] thiazol-3-one **6**, which when treated with hydroxylamine hydrochloride or phenyl hydrazine yielded 6,7-diphenylimidazo[2,1-*b*] thiazolo[2,3-c] oxazole or (*N*-phenylpyrazole) $\mathbf{7}_{c,d}$ with loss of dimethyl amine and a water molecule. The ^{1}H-NMR spectra of $\mathbf{7}_{c,d}$ showed a resonance at δ 9.50 and δ 10.11 corresponding to H-3 of oxazole and H-3 of N-phenylpyrazole. Moreover, the ^{13}C-NMR revealed signals at δ 150.88 and δ 148.00 C-3 in oxazole and N-phenylpyrazole rings. Reactions of **3** with thiophene-2-carbaldehyde in glacial acetic acid and fused sodium acetate gave 5,6-Diphenyl-2 (2-thenylidene) imidazo[2,1-*b*] thiazol-3- one **8**. Compound **3** was reacted with 2-thenylidene malononitrile or 2-thenylidene benzoylacetonitrile in ethanol and piperidine[12] afforded 7,8-diphenyl imidazo [2,1-*b*] thiazolo [2,3-*b*] pyran derivatives $\mathbf{9}_{e,f}$. This result is in agreement with the behavior of similarly substituted δ-oxonitrile, which spontaneously cyclized to 2-amino-4H-pyran ring.[13]

Compound $\mathbf{9}_{e,f}$ was obtained by another route by treating **8** with malononitrile or benzoylacetonitrile in ethanol and piperidine.[14] Also, 3,4-dihydro-2-oxo-2H-7,8-diphenyl imidazo[2,1-*b*] thiazolo[2,3-*b*] pyran-3-carbonitrile **10** was formed from compound **3** and 2-thenylidene ethylcyanoacetate in ethanol and piperidine. The IR and ^{1}H-NMR spectra are in agreement with the structure **10**. Further formation of **10** from compound **8** with ethyl cyanoacetate is through a Michael addition. The structures of **8–10** were established on the basis of its elemental analysis and spectral data.

Compound **1** reacted with α-chloroacetylacetone and α-chloro-ethylacetoacetate in pyridine[5] to give 2-acetyl (or 2-ethoxycarbonyl)-3-methyl-5, 6-diphenylimidazo[2,1-*b*] thiazole-$\mathbf{12}_{h,i}$ (Scheme 2). These products were most likely formed via initial formation of non-isolable intermediates $\mathbf{11}_{h,i}$ via dehydrochlorination which then could be cyclized via enolization and loss of water molecule under applied reaction condition to yield $\mathbf{12}_{h,i}$. The structure of $\mathbf{12}_{h,i}$ was proved based on both elemental analysis and spectral data. The IR spectra of $\mathbf{12}_{h,i}$ showed the absorption bands corresponding to carbonyl 1680 cm^{-1} and ester carbonyl 1710 cm^{-1}. The ^{1}H-NMR spectra of $\mathbf{12}_{h,i}$ revealed signals for CH_3, CH_2CH_3 and aromatic protons.

When $\mathbf{12}_h$ was treated with thiophene-2-carbaldehyde in presence of piperidine[15] gave 3-Methyl-5,6-diphenyl-2(2-thenylidene-2-propenoyl) imidazo[2,1-*b*] thiazole $\mathbf{13}_h$. The IR spectrum of $\mathbf{13}_h$ shows absorption at 1680 cm^{-1} (C=O). the ^{1}H-NMR of $\mathbf{13}_h$ showed the CH_3 protons as a singlet at δ 2.11, the HC=CH protons at δ 5.32. The reactions of $\mathbf{13}_h$ with 2-chlorophenyl hydrazine in dioxan and with benzamidine hydrochloride in pyridine gave 2-(1-(2-chlorophenyl)-5-(2-thienyl)pyrazollin-3-yl)-3-methyl-5,6-diphenyl-imidazo[2,1-*b*] thiazole $\mathbf{14}_h$ and 2-[(4-thienyl) 4,5-dihydro-2-phenyl pyrimidine-6-yl)]-3-methyl-5,6-diphenylimidazo [2,1-*b*] thiazole $\mathbf{15}_h$. The IR spectrum of $\mathbf{14}_h$ showed the absence of any absorption in carbonyl region and ^{1}H-NMR showed the (CH_3) protons as a singlet at δ 2.11, the CH_2 protons as singlet at δ 5.50 and the (CH) proton as singlet



Scheme 2.

at δ 4.48, while IR spectrum of **15**$_h$ showed absence of carbonyl group and presence of NH absorption band at 3220 cm^{-1} and ^{1}H-NMR spectrum showed two singlet at δ 5.20 for (CH) pyrimidine and at δ 8.21, CH-pyrimidine and singlet at δ 11.50 for (NH) group.

Subsequent refluxing of **12**$_h$ with hydroxylamine or hydrazine hydrate in methanol[16] gave 3a(1H)-3,9-dimethyl-6,7-diphenylimidazo [2,1-*b*] thiazolo[4,5-d] isoxazole **16**$_j$ and 1,3a-dihydro-3,9-dimethyl-6,7-diphenylimidazo[2,1-*b*] thiazolo[3,4-d] pyrazole **16**$_k$. The ^{1}H-NMR spectrum of **16**$_j$ showed signals at δ 1.40 (CH_3), 2.00(CH_3), 4.00 (s, 1H, 3a-H) and broad single at 7.70 (NH). The ^{1}H-NMR spectrum for **16**$_k$ showed at δ 1.32(CH_3), δ 1.93(CH_3), 4.00 (s, 1H, 3a-H) and δ 9.11(NH) group.

Conclusion

The synthesized compounds are of imidazo [2,1-b] thiazole, imidazo [2,1-b] thiazolo [2,3-b] pyran or (pyron), imidazo [2,1-b] thiazolo [2,3-c] oxazole or (N-phenyl pyrazole) and imidazo [2,1-b] thiazolo [4,5-b] isoxazole derivatives act as potent antibacterial and antifungal compounds. Thus 7,8-diphenyl imidazo[2,1-b] thiazolo[2,3-b] pyran-2-ethoxycarbonyl(or carboxylicacid)-4-one 5a,b are an acceptable potent compound inhibiting Gram-positive bacteria. Most of tested compounds showed activity toward fungi.

Experimental

All melting points were recorded on Gallenkamp melting apparatus and uncorrected. The IR spectra were recorded on a pye- unicam SP-3-100 spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz with DMSO-d_6 as solvent and tetramethyl silane as an internal standard, chemical shifts are expressed as δ unit (ppm). The mass spectra were recorded on Ms S 988 operating to 70 eV. Elemental analysis was determined using a Perkin-Elmer 240C microanalyses.

2-S-methyl carboxylic acid-4, 5-diphenyl imidazole 2

A solution of **1** (0.01 mol) and **(chloroacetic)** acid (0.01 mol) in a mixture of 20% ethanolic KOH solution (20 mL) was heated under reflux 5 hours. The reaction mixture was cooled and poured onto ice-cold water. The solid product obtained after acidification with concentrated HCl, washed with water and recrystallized from ethanol, (110–112) °C; 70%. yield; υ_{max}/cm^{-1} (KBr); 3400 (NH), 3200–3000

Table I. Biological screening of the selected compounds on some bacteria and fungus.

Compound no.	Staphylococcus aureuss (+ve)	Bacillus cereus (+ve)	Sarraha (–ve)	Pseudomonas (–ve)	Yeast (fungi)
2	–	–	–	–	–
3	–	–	–	–	0.5
4	–	0.7	–	–	0.9
5_a	0.6	–	–	–	1.00
5_b	–	0.8	–	–	–
6	–	–	–	–	–
$7_{c,d}$	–	–	–	–	–
8	–	–	–	–	0.7
9_e	–	–	–	–	0.7
9_f	–	–	–	–	–
10	–	0.6	–	–	1.1
12_h	–	–	–	–	–
12_i	–	–	–	–	–
13_h	–	–	–	–	0.5
14_h	–	–	–	–	–
15_h	–	–	–	–	0.9
16_i	0.8	–	–	–	–
16_k	–	–	–	–	0.5
Clotrimazol	3	2	1.9	1.8	1.5

(–) No significant inhibition.

(br-OH), 3055(CH.arom.), 2970 (CH.aliph), 1690 (C=O), 1630 (C=N); δ_H (DMSO-d_6) 2.80 (s, 2H, CH_2), 7.50–8.00 (m, 10H, Ar-H), 10.20 (s, 1H, NH), 13.11 (s, 1H, OH). Anal. Calcd. For $C_{17}H_{14}N_2O_2S$: C, 65.80; H, 4.51; N, 9.03; S, 10.32. Found: c, 65.82; H, 4.30; N, 9.00; S, 10.50.

5,6-Diphenyl imidazo [2,1-*b*] thiazole-3-one 3

Method A

To a stirred solution of **2** (0.01 mol) in absolute ethanol (50 mL), a few drops of ethanolic sodium ethoxide were added. The stirring was continued for 15 min and then the reaction mixture was refluxed for another 15 min. The separated solid product was filtered off and recrystallized from ethanol, m.p. (210–212) °C; 85%. yield; υ_{max}/cm^{-1} (KBr); 3050 (CH–arom.), 2900 (CH.aliph.), 1700 (C=O), 1640(C=N); δ_H (DMSO-d_6) 4.00(s, 2H, CH_2), 7.00–7.40(m, 10H, Ar–H); m/z = 276. Anal. Calcd. For: $C_{17}H_{12}N_2OS$: C, 73.91; H, 4.34; N, 10.14; s, 11.59. Found: C, 74.00; H, 4.30; N, 10.00; S, 11.70.

Method B

A mixture of **1** (0.01 mol) and chloroacetic acid (0.01 mol) in acetic acid (15 ml) was reflexed for 3 hours in the presence of anhydrous sodium acetate (5 g). The solid product obtained were filtered off washed with water and recrystallized from ethanol.

2- Acetyl-3-hydroxy-5,6-diphenylimidazo[2,1-*b*]thiazole 4

A mixture of **3** (0.4 moles), anhydrous sodium acetate (100 g) and acetic anhydride (120 mL) was stirred and heated under reflux for an one hour. The cooled reaction mixture was poured onto 700 g of crushed ice and extracted with chloroform (3 × 200 mL). The chloroform extract was washed with cold 5% sodium hydroxide (3 × 500 mL). The aqueous extracts were combined and acidified with 5% hydrochloric acid. The solid product was collected by filtration and recrystallized from ethanol, m.p. (300–303) °C; 80%. yield; υ_{max}/cm^{-1} (KBr); 3200(br.OH), 3055(CH-arom.), 2900(CH-aliph.), 1630 (C=O with H–bonding), 1600(C=C); δ_H (DMSO-d_6)2.28(s, 3H, CH_3), 7.20–7.55 (m, 10H, Ar–H), 13.20 (br, 1H, OH); m/z = 334. Anal. Calcd. For: $C_{19}H_{14}N_2O_2S$; C, 68.26; H, 4.19; N, 8.38; S, 9.58. Found: C, 68.50; H, 4.20; N, 8.52; S, 9.30.

7,8-Diphenyl imidazo[2,1-*b*] thiazolo [2,3-*b*] pyran-2-ethoxycarbonyl (or carboxylic acid)-4-one 5a,b

Method A

A mixture of sodium (1.38 g) in ethanol (40 mL) was heated under reflux until sodium was dissolved. Then 0.03 mole of **4** was added in one hour followed by addition of (30 m moles) of diethyl oxalate. The mixture was heat under reflux for another 2 hours, cooled and (3 mL) of concentrated sulfuric acid was cautiously added after heating at 60–70º on a water bath for one hour. The reaction mixture was cooled and 200 g of crushed ice was added. The mixture filtered and the precipitate dried and recrystallized from ethanol to give 5a and the hydrolyzed acid **5b**: **5a**: m.p. (>360) °C; 60%. yield; υ_{max}/cm^{-1} (KBr); 3040(CH–arom.) 2700–2900(CH–aliph), 1740 (C=O ester), 1665 (C=O) pyrone, 1135 (C–O–C) pyrone, 870(C–H pyrone); δ_H (DMSO–d_6) 1.20 (t, 3H, CH_3CH_2), J = 10.00 Hz), 4.30 (q, 2H, CH_2CH_3, J = 11.20 Hz), 6.98 (s, 1H, H–3), 7.25–7.60(m, 10H, Ar–H); ^{13}C NMR (DMSO–d_6): δ = 19.00 (CH_3), 40.22 (CH_2), 130.11, 130.90, 132.00, 132.87, 133.30, 134.82, 135.11, 135.50 138.80, 140.22, 141.32 and 200.00 (C=O pyrone) Anal: Calcd. for: $C_{23}H_{16}N_2O_4S$: C, 66.34; H, 3.84; N, 6.73; S, 7.69. Found: C, 65.54; H, 4.00; N, 700; S, 8.00.

Method B: for preparation 5b

A mixture of ester **5**a (1 g) and a mixture of concentrated hydrochloric acid (20 mL) and glacial acetic acid (1:1) was heated on a water bath for one hour. The resulting mixture was poured onto 100 g of crushed ice and the precipitate was collected, dried and recrystallizd from acetic acid, m.p. (180–182) °C; 45%. yield; υ_{max}/cm^{-1} (KBr); (3150–2800) (br-OH), 3055(CH–arom.), 1705 (C=O), 1660 (C=O) pyrone, 1600 (C=C),1170 (C–O–C) pyrone, 930(C–H) pyrone; δ_H (DMSO–d_6) 6.00 (s, 1H, H–3), 7.50–7.88 (m, 10H, Ar–H); ^{13}C NMR (DMSO–d_6): δ = 133.11, 133.80, 134.33, 135.11, 135.50, 136.21, 136.90, 137.77, 138.30, 139.40, 139.78 and 168.50 (C=O), 204.00 (C=O) pyrone. Anal: Calcd. for: $C_{21}H_{12}N_2O_4S$: C, 64.94; H, 3.09; N, 7.21; S, 8.24. Found: C, 65.01; H, 3.00; N, 7.48; S, 8.53.

2-Dimethyl-aminomethylene-5,6-diphenylimidazo[2,1-*b*]thiazol-3-one 6

A mixture of **3** (0.01 mol) and dimethyl formamide dimethylacetal (DMFDMA) (0.01 mol) was fused at room temperature for 2 hours and the reddish orange paste, so formed, was washed with acetone. The product was collected and recrystallized from ethanol, m.p. (170–172) °C; 50% yield; υ_{max}/cm^{-1} (KBr; 3055 (CH–arom.), 2750–2980 (CH–aliph.), 1700 (C=O); δ_H (DMSO–d_6) 2.31 (s, 6H, NMe_2), 7.00–7.98 (m, 1H, CH–olefinic, Ar–H). Anal. Calcd. for: $C_{20}H_{17}N_3OS$: C, 69.16; H, 4.89; N, 12.10; S, 9.22. Found: C, 69.12; H, 4.90; N, 12.00; S, 9.38.

6,7-Diphenyl imidazo[2,1-*b*] thiazolo[2,3-c] oxazole (or N-phenyl—pyrazole) 7c,d

A mixture of **6** (10 m mol) and hydroxylamine hydrochloride or phenylhydrazine (10 mmol) in ethanol (30 ml) was refluxed for 7 hours and left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from dioxan. **7**$_c$, m.p. (280–282 °C; 85% yield; υ_{max}/cm^{-1} (KBr); 3065 (CH–arom.), 1645(C=N); δ_H (DMSO-d_6) 7.50–8.11 (m, 10H, Ar–H), 9.50 (s, 1H, H–3);^{13} CNMR (DMSO–d_6) C-aromatic: δ 120.11, 123.35, 125.00, 128.32, 129.92, 130.18, 130.92, 133.40, 134.00, 138.12 and 150.88 (C–3); m/z = 317. Anal. Calcd. for: $C_{18}H_{11}N_3OS$: C, 68.13; H, 3.47; N, 13.24; S, 10.09. Found: C, 68.00; H, 3.66; N, 13.11; S, 10.00. **7**d: m.p. (130–133) °C; 50% yield; υ_{max}/cm^{-1}(KBr); 3060 (CH–arom.), 1640 (C=N); δ_H (DMSO–d_6) 7.33–8.0, (m,15H, Ar–H), 10.11 (s, 1H, CH–pyrazole);^{13} CNMR (DMSO–d_6) δ 120.00, 121.11, 121.99, 123.12, 123.50, 124.12, 125.06, 126.66, 127.00, 128.80, 129.03, 129.77, 130.13, 132.77, 133.08, 134.22, 135.18 and 148.00 (C-3). Anal. Calcd. for: $C_{24}H_{16}N_4S$: C, 73.46; H, 4.08; N, 14.28; S, 8.16. Found: C, 73.50, H, 4.00; N, 14.50; S, 8.11.

5,6-Diphenyl-2-(2-thenylidene) imidazo[2,1-*b*]thiazole-3-one 8

A mixture of **3** (0.01 mol), fused sodium acetate (3 g) and thiophene-2-carbaldehyde (0.01 mol) in glacial acetic acid 25 mL was refluxed for 2 hours. The reaction mixture was cooled, powered over cold water, then the separated solid was filtered, washed with water

and recrystallized from ethanol m.p. (180–182)°C; 70% yield; υ_{max}/cm^{-1} (KBr) 3044 (CH–arom.), 1690(C=O); δ_H (DMSO–d_6) 7.20–7.88 (m, 1H, CH olefinict, Ar–H). Anal: Calcd. for: $C_{22}H_{14}N_2OS_2$: C, 68.39; H, 3.62; N, 7.25; **(S)**, 16.58. Found: C, 68.62; H, 3.78; N, 7.10; S, 16.60.

7,8-Diphenylimidazo[2,1-*b*]thiazolo[2,3-*b*] pyran derivatives 9e,f, 10

Method A

A mixture of **3** (5 mmol), 2-thenylidene activated nitrile (5 mmol) and piperidine (0.5 ml) in ethanol (30 ml) was refluxed for 6 hours. The reaction mixture was then triturated with water. The resulting solid was collected by filtration, recrystallized from dioxan and ethanol, **9**e: m.p. (>360)°C; **(75%)** yield; υ_{max}/cm^{-1} (KBr) 3320, 3180 (NH_2), 3060 (CH. arom.) 2210 (CN), 1610(C=C); δ_H (DMSO–d_6) 4.40 (s, 1H, H–4), 6.50 (s, 2H, NH_2), 7.11–7.79 (m, 13H, Ar–H). Anal. Calcd. for: $C_{25}H_{16}N_4OS_2$; C, 66.37; H, 3.53 N, 12.38; s, 14.15. Found: C, 66.80; H, 3.50; N, 12.66, S, 14.80. **9**$_f$: m.p. (150–152) °C, 55% yield; υ_{max}/cm^{-1}(KBr); 3310, 3200(NH_2), 3065 (CH–arom.), 1680(C=O). δ_H (DMSO–d_6) 4.27 (s, 1H, H-4), 5.80 (s, 2H, NH_2) 6.80–7.90 (m, 18H, Ar–H); m/z = 531. Anal. Cacld. for: $C_{31}H_{21}N_3O_2S_2$; C, 70.05; H, 3.95; N, 7.90; S, 12.05 Found: C, 70.00; H, 3.28; N, 8.08; S, 12.00.

10: m.p. (170–172) °C; 50% yield; υ_{max}/cm^{-1}(KBr); 3070(CH-arom.), 2900 (CH aliph.), 2240 (C≡N), 1710(C=O); δ_H (DMSO–d_6) 4.20 (d, 1H, CH, J = 5.44 Hz), 4.50 (d, 1H, CH, J = 6.24 Hz), 7.30–7.82 (m, 13H, Ar–H). Anal. Calcd. for: $C_{25}H_{15}N_3O_2S_2$: C, 66.22; H, 3.31; N, 9.27; S, 14.12. Found: C, 66.30; H, 3.58; N, 9.30; s, 14.50

Method B for preparation 9$_{e,f}$ and 10

A solution of compound 8 (5 mmol) in ethanol (30 ml), activated nitrile (5 mml) and piperidine (0.5 ml) was refluxed for 3 hours. The reaction mixture was poured into ice-H_2O and acidified with dilute HCl. The resulting solid was filtered and recrystallized from dioxin and ethanol.

2-Acetyl (or-ethoxycarbonyl)-3-methyl-5,6-diphenylimidazo[2,1-*b*] thiazole 12$_{h,i}$

A solution of **1** (0.01 mole) and α-chloroacetylacetone or α-chloroethylacetoacetate (0.01 mol) in pyridine (20 ml) was heated under reflux for 5 hours. The reaction mixture was cooled and poured onto ice-cold water. The solid products obtained after acidification with concentrated HCl, washed with water and recrystallized from ethanol, **12**$_h$: m.p. (140–142) °C; 65% yield; υ_{max}/cm^{-1}(KBr); 3070 (CH. arom.), 2880 (CH. aliph.), 1680 (C=O), 1590 (C=C); δ_H (DMSO–d_6); 2.10 (s, 3H, CH_3), 2.42 (s, 3H, CH_3CO), 7.20–7.52 (m, 10H, Ar–H); m/z = 332; Anal. Calcd. for: $C_{20}H_{16}N_2OS$: C, 72.28; H, 4.18; N, 8.43, S, 9.63. Found: C, 72.72; H, 4.98; N, 8.50; s, 9.88.

12$_i$; m.p. (210–212) °C; 55% yield; υ_{max}/cm^{-1}(KBr); 3075 (CH–arom.); 2775–2888(CH–aliph.), 1710 (C=O) ester, 1620(C=C); δ_H (DMSO–d_6) 1.10 (s, 3H, CH_3), 1.40 (t, 3H, CH_3CH_2, J = 9.11 Hz), 4.50 (q, 2H, CH_2, J = 10.00 Hz) 7.38–7.80 (m, 10H, AH); m/z = 362. Anal. Calcd. for: $C_{21}H_{18}N_2O_2S$: C, 69.61; H, 7.97; N, 7.73, S, 8.83. Found: C, 69.60; H, 4.88; N, 7.70; S, 8.98.

3-Methyl-5,6-diphenyl-2(2-thienylidene-2-propenoyl) imidazo[2,1-*b*]-thiazole 13$_h$

A mixture of **12**$_h$ (0.01 mol) and thiophene-2-carbaldehyde (0.015 mol) in the presence of catalytic piperidene (0.5 ml) was heated under reflux for 2 hours, cooled and triturated with ethanol. The precipitate obtained was filtered and recrystallized from acetic acid, m.p. (>360) °C; 80% yield; υ_{max}/cm^{1-} (KBr); 3080 (CH-arom.), 2900 (CH. aliph.), 1680 (C=O), 1600 (C=C); δ_H (DMSd_6) 2.11 (s, 3H, CH_3), 5.32 (m, 2H, HC=CH), 7.40–8.00 (m, 13H–Ar–H) Anal. Calcd. For: $C_{25}H_{18}N_2OS_2$: C, 70.42; H, 4.22; N, 6.57; S, 15.02. Found: C, 70.50; H, 4.66; N, 6.60, S, 15.00.

2-(1-(2-chlorophenyl)-5-(2-thienyl) pyrazollin-3-yl)-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole 14$_h$

A mixture of **13**$_h$ (0.005 mol) and 2-chlorophenyl hydrazine (0.5 ml) in dioxan (20 ml) was heated under reflux 6 hours and left overnight. The precipitate formed was collected and recrystallized from ethanol, m.p. (300–302) °C; 70% yield υ_{max}/cm^{-1}(KBr); 3060 (CH–arom.), 2900 (CH-aliph.); δ_H (DMSO–d_6) 2.11 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 4.48 (s, 1H, CH), 7.50–8.00 (m, 17H, Ar–H); m/z = 550.

Anal. Calcd. for: $C_{31}H_{23}N_4ClS_2$: C, 67.57; H, 4.17; N, 10.17; S, 11.62; Cl, 6.44. Found: C, 67.80, H, 4.90; N, 10.50; S, 11.95; Cl, 6.50.

2-(4-thienyl)4,5-dihydro-2-phenyl pyrimidine-6-yl)-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole 15_h

A solution of $\mathbf{13}_h$ (0.01 mol) and benzamidine hydrochloride (0.01 mol) in pyridine (20 ml) was heated under reflux for 6 hours and left overnight. The precipitate formed was collected and recrystallized from ethanol-benzene, m.p. (100–103) °C, 50% yield; υ_{max}/cm^{-1}(KBr); 3220 (NH), 3075 (CH-arom.), 2990 (CH-aliph.), 1610 (C═C), 1645 (C═N); δ_H (DMSO–d_6); 1.43 (s, 3H, CH_3), 5.20 (s, 1H, CH), 7.20–8.00 (m, 18H, Ar–H), 8.21(s, 1H,Cpyrimidine), 11.50 (s, 1H, NH); m/z = 528. Anal. Calcd. for: $C_{32}H_{24}N_4S_2$: C, 72.72; H, 4.54; N, 10.60; S, 12.12. Found: C, 72.80; H, 4.33; N, 10.42, S, 12.00.

3a(1H)-3,9-dimethyl-6,7-diphenylimidazo[2,1-*b*]thiazolo [4,5-*b*] isoxazole 16_j

A solution of $\mathbf{12}_h$ (10 mmol) and hydroxylamine hydrochloride (10 m mol) was refluxed in (1 ml) pyridine and (50 ml) methanol for 12 hours. The mixture was evaporated and the residue crystallized from ethanol, m.p. (210–212) °C; 85% yield; υ_{max}/cm^{-1}(KBr); 3090 (Carom.), 2990 (CH.aliph), 1645 (C═N); δ_H (DMSO-d_6); 1.40 (s, 3H, 9a–CH_3), 2.00 (s, 3H, CH_3), 4.00 (s, 1H, 3a–H), 6.90–7.54 (m, 10H, Ar–H), 7.70 (s, 1H, NH);[13] CNMR (DMSO–d_6); 13.18 (9a-CH_3), C-aromatic: 128.00, 128.50, 130.11, 130.95, 132.22, 133.90, 134.15, 135.00, 137.82, 138.11, 139.40.; m/z = 347. Anal. Calcd. for: $C_{20}H_{17}N_3OS$: C, 69.16; H, 4.89; N, 12.10; S, 9.22. Found: C, 69.30; H, 4.80; N, 12.30, S, 9.00.

1,3a-dihydro-3,9-dimethyl-6,7-diphenylimidazo[2,1-*b*] thiazolo[3,4-d] pyrazole 16_k

An analogous procedure led to $\mathbf{16}_k$ from $\mathbf{12}_h$ and hydrazine hydrate (without pyridine). The solid product was collected and recrystallized from ethanol m.p. (300–303) °C; 75 yield; υ_{max}/cm^{-1}(KBr); 3077 (CH-arom.), 2900 (CH-aliph.), 1640 (C═N); δ_H (DMSO–d_6); 1.32 (s, 3H, CH_3, 9a-CH_3), 1.93 (s, 3H, 3-CH_3), 4.00 (s, 1H, 3a-H), 6.88–7.68 (m, 10H, Ar–H), 9.11 (s, 1H, NH);[13] CNMR (DMSO-d_6) δ 14.52 (9a-CH_3), 28.8 (3-CH_3), 58.30 (C–3a) and C-aromatic 125.15, 126.30, 126.98, 127.00, 127.30, 128.11, 129.39, 130.18, 131.12, 133.09; m/z = 346. Anal. Calcd. for $C_{20}H_{18}N_4S$: C, 69.36, H, 5.20; N, 16.18; S, 9.24. Found: C, 69.77, H, 5.50; N, 16.78; S, 9.56.

Biological Activity

The microdilution susceptibility test[17] was used for the determination of antibacterial and antifungal activities. The utilized test organisms were: Staphylococcus aureus, Bacillus cereus as an example of gram-positive bacteria; Sarraha, Pseudomonas as gram-negative bacteria and yeast- like fungus. Clotrimazole was used as standards antibacterial and antifungal agents. The strains were maintained on nutrient agar medium. The test compounds were dissolved in nutrient broth (DIFCO) medium at a concentration of 50 µg/ml and 2 ml of nutrient culture of the bacterial strain to be was added at 10^6 CFU/ml (colony forming unit/ml). The cultures were incubated overnight at 37 C. Most of the tested compounds showed activity toward fungi while many of these did not have activity toward bacteria.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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